DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

m2198n

NOV 13 1998

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. David Keini, President
Omiderm Ltd.
P.O. Box 422
5 Shidlowsky Street
New Industrial Zone
Yavne, Israel 70653

Dear Mr. Keini:

During an inspection of your firm located in Yavne, Israel on August 16 through 18, 1998, our investigator determined that your establishment manufactures sterile surgical wound dressings. These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above stated inspection revealed that these devices are adulterated under Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the good manufacturing practice (GMP) requirements of the Quality System Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Failure to validate the process with a high degree of assurance when the result of a process cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). For example:

   a. Product [2 words deleted] studies for the [2 words deleted] sterilization process are inadequate because they were performed for only one of the production sterilization loads.

      Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

   b. The package sealing process has not been validated to establish routine operating parameters such as temperature, pressure, and dwell time.

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

2. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50. For example:

   a. There is no knowledge of process control and quality assurance procedures at the contract sterilizer. No formal evaluation nor vendor audits have been conducted.

      Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by November 30, 1998.

   b. There are no procedures specifying the location of [illegible] in sterilization loads to be [illegible] by the contract sterilizer.

      Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by November 30, 1998.

   c. Process control procedures have not been established with the contract sterilizer for such controls as sterilization lot processing specifications, procedures required following out-of-specification results or process interruptions, required communications and records, and for other controls that could impact on the achievement of sterility for the product sent for sterilization.

      Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by November 30, 1998.

3. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications and to establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications including documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production, as

required by 21 CFR 820.70(a)(1). For example, results of the [3 words deleted] were not translated into procedures for placement of [1 word] used to measure [5 words deleted] for routine sterilization lots. The contract sterilizer has not been instructed on [2 WORDS deleted].

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by November 30, 1998.

4. Failure to establish and maintain procedures for implementing corrective and preventive action including requirements for investigating the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(2). For example, there are no established procedures for handling out-of-specification test results. Test methods for [4 words deleted] allow documentation for out-of-specification test results to be discarded without investigation and determination of the cause. Lots are released if a retest passes.

   Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

5. Failure to establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR 820.80(d). For example:

   a. There is no knowledge of actual placement of [6 words deleted] readings for release of product as sterile following [1 word] sterilization performed by a contract sterilizer.

      Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by November 30, 1998.

   b. The only packaging tests conducted after sterilization consisted of a [9 words deleted 6 words deleted] has not been challenged.

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

c. For example, records are not maintained demonstrating the quality control tests [4 words deleted] were conducted within required parameters for temperature and relative humidity.

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 20, 1998.

6. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications including monitoring and control of process parameters and component and device characteristics during production, as required by 21 CFR 820.70(a)(2). For example, on August 16, 1998, the packaging machine was operating at [ ]C, below the specified [ ]'C; the dwell time was documented at [ ]seconds at 1:00 pm, but was noted at[ ]seconds at 3:00 pm, above the specified[ ]second range and no entries were recorded for pressure. The pressure is specified at[ ] and was observed at [ ]

Your response is not adequate because it provided no evidence of correction.

7. Failure to maintain device master records which include, or refer to the location of production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications, as required by 21 CFR 820.181(b). For example:

a. In the clean room, there are no established specifications for [— 14 words deleted —]

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 30, 1998.

b. The diagram for the water system used to process the wound dressings does not reflect the new [

[17 words deleted]

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 30, 1998.

8. Failure to establish and maintain procedures to adequately control environmental conditions where environmental conditions could reasonably be expected to have an adverse effect on product quality, as required by 21 CFR 820.70(c). For example:

   a. Laminar flow from [ ] HEPA filters is blocked by trays installed [3 words] under the filters 1) over the [1 word] line where employees are [6 words deleted], and 2) over the table where in-process product [4 words deleted]

   Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 31, 1998.

   b. The design of the dressing room precludes setting up the room to separate a side for dressing from a side for entering the [3 words deleted] room.

   Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 31, 1998.

   c. There is no established standard operating procedure (SOP) or facility construction which precludes simultaneously opening both the door from the [ ] room to the clean room and from the dressing room to the [ ] room.

   Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 31, 1998.

   d. The out-of-service [2 words] remains in the water system loop.

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 31, 1998.

9. Failure to establish and maintain procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a). For example, product design and packaging changes were made [ ] without documentation, justification, evaluation, or validation.

   Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

10. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a). For example, the customer complaint SOP does not require distributors to supply complaint information and customer files are not screened for complaints.

    Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

11. Failure to evaluate complaints to determine whether the complaint represents an event which is required to be reported to FDA under 21 CFR part 803 or 804, Medical Device Reporting, as required by 21 CFR 820.198(a)(3). For example, the customer complaint SOP does not include procedures for Medical Device Reporting.

    Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by October 30, 1998.

12. Failure to establish and maintain procedures for the use and removal of manufacturing material where the material could reasonably be expected to have an adverse effect on product quality, as required by 21 CFR 820.70(i). For example, procedures for monitoring water used for [4 words deleted] are inadequate in that:

    a. Required tests for [4 words deleted] were not conducted in 1998 and out-of-specification [1 word] test results ([4 words] in September 1997) and ([4 words deleted] in

November 1997) were not identified or investigated. Specifications establish [3 words deleted] as an action limit.

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 31, 1998.

b. Specifications for [5 words deleted] have not been met. Test results are expressed in units which do not correlate with specifications.

Your response is not adequate because it provided no evidence of correction. You stated that corrective action would be completed by December 30, 1998.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and the FDA 483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

In order to facilitate FDA in making the determination that such corrections have been made and thereby enabling FDA to withdraw its advisory to other federal agencies concerning the award of government contracts, we are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the GMP requirements of the Quality System Regulation (21 CFR, Part 820). You should also submit a copy of the consultant's report, and certification by your firm's Chief Executive Officer (CEO) (if other than yourself) that your firm has initiated or completed all corrections called for in the report. The attached guidance may be helpful in selecting an appropriate consultant.

The certification of audits should be submitted to this office by the following date:

- Initial certification by an outside consultant no later than May 15, 1999.

Given the serious nature of these violations of the Act, all devices manufactured by Omiderm Ltd. Yavne, Israel, may be detained upon entry into the United States without physical examination until these violations are corrected.

In order to remove the devices from detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review, and have an outside consultant certify your compliance with the Quality System Regulation no later than May 15, 1999. After we notify you that your response is adequate, it will be your responsibility to schedule an inspection of your facility. As soon as the inspection has taken place, the implementation of your corrections has been verified, your products may resume entry into this country.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for devices to which the GMP deficiencies are reasonably related will be cleared until the violations have been corrected.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations, for each violation in which the response was less than adequate. Please include any and all documentation to show that adequate correction has been achieved. In the case of future corrections, an estimated date of completion, and documentation showing plans for correction, should be included with your response to this letter. If the documentation is not in English, please provide a translation to facilitate our review.

Your response should be sent to Sarah Mowitt at the above letterhead address. If you have questions or need further assistance contact Mrs. Mowitt by telephone at (301) 594-4595 of by FAX at (301) 594-4636.

Sincerely yours,

George Kroehling for

Lillian Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosure: Selecting a Consultant?